REMARKS

Applicants respectfully requests entry of the amendments and remarks submitted herein. Claim 1 has been amended to recite that administration of a 4-1BB agonist to a subject results in depletion of double negative T cells in the subject. Claim 18 has been amended to recite that contacting a double negative T cell with a 4-1BB agonist results in death of the double negative T cell. Support for these amendments can be found throughout Applicants' specification. Claim 7 has been amended to correct a typographical error, and claim 8 has been amended to incorporate the language of claim 9, which has been canceled without prejudice. In addition, pages 6 and 29 of the specification have been amended to replace the term "GR-1" with the term "Gr-1." No new matter has been added.

In light of these amendments and the following remarks, Applicants respectfully request reconsideration and allowance of claims 1-8, 10, 17-21, 23-28, and 32.

Priority Claim

Applicants respectfully disagree with the Examiner's statement that U.S. Provisional Application No. 60/395,896 (the'896 application), from which the present application claims priority, fails to provide adequate support for the step of monitoring the subject for symptoms of a disease, as recited in present claim 17. In fact, the '896 provides several examples of monitoring for symptoms of a disease in a subject treated with a 4-1BB agonist. For example, the Results section at pages 5 to 9 of the '896 application discloses treating mice with a 4-1BB agonist and then monitoring the mice for symptoms of lupus (e.g., lymphadenopathy, skin lesions, renal disease, and autoantibody production). Thus, in contrast to the Examiner's assertion, the '896 application provides adequate support for claim 17.

Restriction Requirement

Applicants respectfully disagree with the Examiner's assertion that Applicants did not provide substantive reasoning or grounds for asserting that the Restriction Requirement was improper. In particular, Applicants note that pages 2 and 3 of the Response to Restriction

Requirement filed on March 22, 2006 presented substantive reasoning for their traversal of the requirement. For example, Applicants asserted that it is improper to require a restriction between claims to a method for depleting double negative T cells in a subject having, or at risk of having, an autoimmune disease, by administering an anti-4-1BB antibody, and claims to an analogous method that includes administering a nucleic acid encoding an anti-4-1BB antibody. Applicants proposed that claims 1 and 18 are linking claims with respect both to the genus of diseases and the genus of 4-1BB agonists, such that species of diseases and agonists could be elected. Nonetheless, Applicants acknowledge the finality of the Restriction Requirement.

Claim objections

The Examiner objected to claim 7 because of an apparent typographical error. The Examiner also objected to claims 8 and 9 because they recite "Gr-1," while the specification appears to refer to the same molecule as "GR-1."

Applicants have amended claim 7 to replace "interferon-K" with "interferon-γ." With regard to claims 8 and 9, Applicants note that the terms "Gr-1" and "GR-1" are used interchangeably in the specification. Thus, what is meant by "GR-1 and "Gr-1" would be clear to a person of skill in the art. Nevertheless, Applicants have amended the specification to replace the term "GR-1" with "Gr-1."

In light of the above, Applicants respectfully request withdrawal of the objection to claims 7 and 8.

Rejections under 35 U.S.C. § 112

The Examiner rejected claims 6, 8, 9, and 21 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. In particular, the Examiner asserted that the claims are indefinite in the recitation of "2A" and "Gr-1," because the characteristics of 2A and Gr-1 are not known.

Applicants respectfully disagree. The recitation of antibody 2A is definite, as characteristics of the antibody are provided in Applicants' specification as described, e.g., in Example 1. Thus, antibody 2A would be identifiable to a person of skill in the art. The

recitation "Gr-1" also is definite. This is particularly true given that Applicants' specification defines Gr-1 as "a myeloid differentiation antigen expressed on cells of the myeloid lineage, and serves as a marker for granulocyte maturation." *See*, page 16, lines 17-21 of Applicants' specification. Thus, the terms "2A" and "Gr-1" are definite.

In light of the above, Applicants respectfully request withdrawal of the rejection of claims 6, 8, and 21 under 35 U.S.C. § 112, second paragraph.

The Examiner rejected claims 6 and 21 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. The Examiner stated that the antibody 2A must be known and readily available to the public or obtainable by a repeatable method set forth in the specification, or that the cell line or hybridoma that produces the antibody must be deposited.

Applicants respectfully disagree. First, this rejection is contrary to the Examiner's statement at page 8 of the outstanding Office Action that the specification is "enabling for methods employing a 4-1BB agonist antibody 2A." Second, a person of skill in the art reading Applicant's specification would be able to carry out the presently claimed methods without undue experimentation. This is particularly true given (a) the well-established, art known methods for producing antibodies, and (b) the teachings of Applicant's specification with regard to methods for making antibodies against 4-1BB and for using such antibodies to deplete double negative T cells by administering them to an appropriate subject. For example, Applicant's specification teaches methods for making polyclonal and monoclonal antibodies at page 8, line 14 to page 9, line 13. In addition, the specification teaches methods for administering a 4-1BB agonist to a subject at, for example, page 15 line 23 to page 16, line 25. That some of such methods were known in the art at the priority date of the instant application is indicated by the citation in Example 1 of the Wilcox *et al.* reference, which describes generation of antibodies to 4-1BB. In fact, a skilled artisan reading Applicants' specification would have been able to generate and select for an antibody that exhibits the double negative T cell-depleting properties of 2A. Thus, given the teachings of Applicants' specification and the knowledge in the art, including the Wilcox *et al.* reference, the present claims are enabled.

In light of the above, Applicants respectfully request withdrawal of the rejection of claims 6 and 21 under 35 U.S.C. § 112, first paragraph.

The Examiner rejected claims 1-9, 17-21, 23-27, and 32 under 35 U.S.C § 112, first paragraph, for alleged lack of enablement. The Examiner asserted that the specification is enabling for a method of depleting, or inducing death of, double negative T cells in a subject having systemic lupus erythematosus (SLE), but does not reasonably provide enablement for depleting, or inducing death of, double negative T cells in a subject matter having a generically recited autoimmune disease, lymphoproliferative disease or allergy. The Examiner further asserted that it is not clear that reliance on the experimental observations described in the specification provide the basis for using antibodies against 4-1BB to treat any autoimmune disease, lymphoproliferative disease, or allergy. In addition, the Examiner alleged that due to insufficient guidance by the specification and the unpredictability in the art, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success for treating a disease other than SLE.

Applicants respectfully disagree. Based on the teachings provided in the specification and the characteristics of the 4-1BB agonists provided, a person having skill in the art would expect that administering an effective amount of such an agonist would deplete or induce the death of double negative T cells in a subject having any of the conditions recited in the present claims, not just SLE. In other words, the ability of the recited 4-1BB agonist to deplete double negative T cells is not dependent on the condition of the subject to which the agonist is administered. The Examiner asserted that the Blazar *et al.* reference demonstrates that issues such as tissue distribution, half-life, affinity and avidity obtained with various antibodies targeting costimulator molecules might prove to be important in achieving a therapeutic effect. Applicants note, however, that such parameters are routinely considered by those of skill in the art in the administration of therapeutic agents. As noted herein, Applicants' specification teaches methods for administering a 4-1BB agonist to a subject, as well as methods for determining whether double negative T cells are depleted in the subject, regardless of the condition of the

subject. Further, the level of skill in the art is quite high. Thus, given the teachings of Applicants' specification and the knowledge in the art, no undue experimentation would be required for a person of skill to carry out the claimed methods for depleting or inducing death of double negative T cells in a subject in need thereof, including a subject having an autoimmune disease, lymphoproliferative disease, or allergy.

In light of the above, Applicants respectfully request withdrawal of the rejection of claims 1-8, 17-21, 23-27, and 32 under 35 U.S.C § 112, first paragraph.

The Examiner rejected claims 1-5, 7-10, 17-20, 23-28, and 32 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. The Examiner asserted that the specification is enabling for methods employing a "4-1BB against antibody 2A," with or without an antibody that binds to Gr-1, but does not reasonably provide enablement for methods employing a generically recited "4-1BB agonist" or "Gr-1 binding agent." The Examiner further asserted that the structures of agonists and binding agents are highly diverse, and that such structures cannot be readily envisioned by one of skill in the art based on the guidance provided in the specification as filed. In addition, the Examiner alleged that it is unclear whether an agonistic 4-1BB-binding agent, and in particular an anti-4-1BB-antibody, would achieve enhancement of an immune response as disclosed in U.S. Publication No. 2005/0013811 (the Chen publication) or suppression of an immune response as recited in the instant claims.

Applicants respectfully disagree. To further prosecution, however, claim 8 has been amended to recite that the Gr-1 binding agent is an antibody that binds to Gr-1. With regard to "4-1BB agonist," Applicants respectfully note that the specification provides guidance for the structures of such agonists. For example, the specification at page 7, lines 19-31 teaches that 4-1BB agonists include 4-1BBL and functional fragments of 4-1BBL, as well as antibodies and antibody fragments that can bind to 4-1BB and potentiate an immune response. A person having skill in the art, reading Applicants' specification, certainly would be able to make and use such agonists. This is particularly true given that the specification teaches how to make 4-1BBL polypeptides and anti-4-1BB antibodies, and also how to test such molecules for the ability to

deplete double negative T cells. *See*, for example, the section of Applicants' specification extending from page 8, line 11 to page 12, line 22, which teaches methods for making polyclonal and monoclonal antibodies, as well as methods for making nucleic acids encoding 4-1BB agonists. *See*, also, the specification at page 17, lines 16-20, as well as Examples 1 and 2 at pages 22-25, which teach that ELISA and flow cytometry can be used to evaluate the ability of a 4-1BB agonist to deplete double negative T cells. Further, as noted above, the specification teaches methods for administering a 4-1BB agonist to a subject. Thus, the teachings of Applicants' specification provide ample guidance for carrying out the claimed methods.

With respect to the Examiner's assertion regarding the Chen publication, Applicants respectfully note that enhancing an immune response is not necessarily the opposite of depleting or inducing death of double negative T cells as recited in the present claims. In fact, Example 2 at pages 24-25 of Applicants' specification discloses that the agonistic antibody 2A activates $CD8^+$ T cells, while reducing the number of $CD4^-/CD8^-$ double negative T cells. Thus, the teachings of Applicants' specification are not inconsistent with the teachings of the Chen publication.

In addition, Applicant respectfully directs the Examiner to *In re Wands* (858 F.2d 731 (C.A.Fed. 1988)), in which the court stated that "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed" (citing *In re Jackson*, 217 USPQ at 807 ((Bd. App. 1982)). Given the guidance provided by Applicants' specification and the high level of skill in the art, it is clear that no undue experimentation would have been required to carry out the presently claimed methods. Thus, the present claims are fully enabled.

In light of the above, Applicants respectfully request withdrawal of this rejection of claims 1-5, 7, 8, 10, 17-20, 23-28, and 32 under 35 U.S.C. § 112, first paragraph.

Rejections under 35 U.S.C. § 102

The Examiner rejected claims 1-5, 17-20, 23-27, and 32 under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 5,928,893 (the Kang *et al.* patent). The Examiner asserted that the Kang *et al.* patent teaches treatment of autoimmune diseases by administering a monoclonal antibody to human 4-1BB. The Examiner further asserted that the Kang *et al.* patent teaches administering an antibody of the same specificity as the instant application to the same patient population as the instant application, and that the functional properties of the antibody and the mechanism of action are inherently the same. With respect to claim 17, the Examiner alleged that treating a disease inherently includes monitoring the symptoms.

Applicants respectfully disagree. The Kang *et al.* patent does not disclose a 4-1BB agonist, as required by the present claims. Rather, the Kang *et al.* patent discloses an anti-human 4-1BB antibody that can inhibit the function of activated T cells and suppress immune responses by blocking the 4-1BB molecule. *See*, for example, the Kang *et al.* patent at column 1, lines 49-55 and column 12, lines 34-42. As such, the antibody disclosed by the Kang *et al.* patent is a 4-1BB antagonist. Further, the antibody of Kang *et al.* is not disclosed to result in depletion of double negative T cells after administration to a subject, as required by present claims 1-5 and 17, or to result in death of double negative T cells, as required by present claims 18-20 and 23-27. Thus, given that the Kang *et al.* patent fails to teach a 4-1BB agonist that can be administered to a subject to deplete double negative T cells or that can induce death of a double negative T cell, this reference does not directly or inherently anticipate the present claims.

In light of the above, Applicants respectfully request withdrawal of the rejection of claims 1-5, 17-20, 23-27, and 32 under 35 U.S.C. § 102(b).

The Examiner rejected claims 1-5, 10, 17-20, 23-28, and 32 under 35 U.S.C. §§ 102(a) and 102(e) as being anticipated by U.S. Patent No 6,303,121 (the Kwon patent). The Examiner asserted that the Kwon patent teaches monoclonal antibodies against human 4-1BB that can be used to suppress T cell proliferation and activation, and can be used to treat SLE. The Examiner further asserted that the Kwon patent teaches administering a functionally equivalent antibody to

4-1BB to the same patient population as the instant application, and that the mechanism of action is inherently the same as that of the instantly recited antibodies. With respect to claim 17, the Examiner again alleged that treating a disease inherently includes monitoring the symptoms.

Applicants respectfully disagree. The Kwon patent does not teach all of the elements recited in the present claims. For example, independent claim 1 recites that administration of a 4-1BB agonist to a subject results in depletion of double negative T cells in the subject, while independent claim 18 recites that contacting a double negative T cell with a 4-1BB agonist results in death of the double negative T cell. The Kwon patent fails to teach using a 4-1BB agonist to produce such an effect. In fact, at no point does the Kwon patent disclose that a 4-1BB agonist has any effect on $CD4^-$ or $CD8^-$ T cells, let alone an effect on T cells that are $CD4^-$ and $CD8^-$ (i.e., double negative). Further, Applicants respectfully submit that the Examiner's assertion regarding the inherent mechanism of action of the Kwon antibody is incorrect. The fact that two antibodies bind specifically to the same target, in this case 4-1BB, does not necessarily mean that both antibodies will have the same effect. In the present case, there is no evidence that the antibodies disclosed by the Kwon patent have the effect of depleting or inducing death of double negative T cells. Applicants further disagree with the Examiner's allegation with respect to claim 17. Simply administering a therapeutic agent to a subject having a particular condition does not necessarily mean that that symptoms of the condition will be monitored. Thus, given the above, the Kwon patent does not disclose, either directly or inherently, a method for using a 4-1BB agonist as recited in the present claims. As such, the present claims are novel over the Kwon patent.

In light of the above, Applicants respectfully request withdrawal of the rejection of claims 1-5, 10, 17-20, 23-28, and 32 under 35 U.S.C. §§ 102(a) and 102(e).

In further light of the above, Applicants respectfully disagree with the Examiner's comments regarding the art made of record and not relied upon in the outstanding Office Action.

CONCLUSION

Applicants submit that claims 1-8, 10, 17-21, 23-28, and 32 are in condition for allowance, which action is respectfully requested. The Examiner is invited to telephone the undersigned agent if such would further prosecution.

Please charge $510 for the Petition for Extension of Time fee, and apply any other charges or credits, to deposit account 06-1050.

Respectfully submitted,

Date: December 7, 2006

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